



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/445, 31/5375, A61P 3/00, 25/00, 25/08, 25/16, 25/28, 9/10, A61K 31/70		A1	(11) International Publication Number: WO 00/62780
			(43) International Publication Date: 26 October 2000 (26.10.00)
(21) International Application Number: PCT/GB00/01563 (22) International Filing Date: 20 April 2000 (20.04.00) (30) Priority Data: 9909064.9 20 April 1999 (20.04.99) GB (71) Applicant (for all designated States except US): OXFORD GLYSCSCIENCES (UK) LIMITED [GB/GB]; 10 The Quadrant, Abingdon Science Park, Abingdon OX14 3YS (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): WALKLEY, Steven [US/US]; Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461 (US). HOLT, Gordon, D. [US/US]; 4 Sparrow Valley Court, Gaithersburg, MD 20879 (US). (74) Agents: LEE, Nicholas, John et al.; Kilburn & Strode, 20 Red Lion Street, London WC1R 4PJ (GB).		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: USE OF GLUCOSYLCERAMIDE SYNTHESIS INHIBITORS IN THERAPY			
(57) Abstract			
<p>The present invention relates to the treatment of conditions such as Niemann-Pick C storage disease, Alzheimer's disease, epilepsy, stroke and Parkinson's disease, and in particular to the use of inhibitors of glucosylceramide synthesis in such treatment. Preferred inhibitors of glucosylceramide synthesis are imino sugar-structured, and include N-butyldeoxynojirimycin (NB-DNJ), N-butyldeoxygalactonojirimycin (NB-DGJ) and N-nonyldeoxynojirimycin (NN-DNJ).</p>			

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

USE OF GLUCOSYLCERAMIDE SYNTHESIS INHIBITORS IN THERAPY

The present invention provides the use of inhibitors of glycolipid synthesis in the manufacture of medicaments for use in the treatment of conditions such as Niemann-Pick C storage disease, Alzheimer's disease, epilepsy, stroke and Parkinson's disease. In particular, the use of N-butyldeoxynojirimycin is provided.

Niemann-Pick Type C (NPC) disease, which is also known as Niemann-Pick disease with cholesterol esterification block, is an autosomal recessive storage disorder of cholesterol metabolism. NPC patients generally appear normal for the first few years of life. However, organomegaly of the liver and spleen soon emerge, and may result in jaundice or other symptoms of dysfunction. NPC patients also gradually develop neurologic abnormalities such as ataxia, tremors, seizures, and loss of speech, cognitive and motor skills, and difficulty with upward and downward eye movements. Impairment progresses, particularly resulting from increasing neural degeneration, and death usually occurs by 5-15 years of age.

Vanier *et al.* (1991) reported that Niemann-Pick Type C is heterogeneous, suggesting the possibility that more than one genetic mutation gives rise to the disease. Molecular studies recently substantiated this possibility. A gene most commonly mutated in Niemann-Pick Type C patients has been identified as NPC1 and mapped to 18q11-q12 (Carstea *et al.*, 1997). The NPC1 gene encodes a protein of 1,278 amino acids, and bears some sequence homology to the putative sterol-sensing regions of SREBP cleavage-activating protein and 3-hydroxy-3-methylglutaryl coenzyme A reductase (Carstea *et al.*, 1997). A specific function for the NPC1 gene product is unknown at this time, although biochemical studies are suggestive that NPC1 gene mutations somehow disturbs cholesterol metabolism. For example, NPC cells are blocked in cholesterol

esterification, but also do not effectively translocate cholesterol from lysosomes to other intracellular organelles (Pentchev *et al.* 1985, Sokol *et al.*, 1988).

Evidence for a second possible gene mutated in Niemann-Pick type C has been
5 described, although it has not yet been identified (Steinberg *et al.*, 1994). Patients with
NPC1 mutations have been subclassified as having Niemann-Pick type C1 disease, while
patients with other mutated gene(s) as having Niemann-Pick type C2 disease. There is
no known difference between the clinical courses of type C1 and C2 patients, and they
appear to respond in the same way to disease treatments. In addition, the C1/C2
10 subclassification is not universally applied. Therefore, Niemann-Pick Type C diseases
originating from NPC1 or other gene mutations are collectively referred to as NPC here.

Biochemical findings for NPC patients show a marked accumulation of cholesterol in the
liver and spleen. The liver and spleen show elevated sphingomyelin levels. However,
15 sphingomyelinase activity remains normal in these tissues. This finding distinguishes
NPC from Niemann-Pick Types A and B diseases which are caused by lysosomal
sphingomyelinase mutations, and so present with markedly reduced levels of this
enzyme.

20 In addition to the liver and the spleen, other cells of NPC patients store cholesterol as
well. For example, bone marrow cells take on a characteristic foamy appearance due to
the presence of large numbers of storage inclusions, while eye and skin cells typically are
less affected. Neuronal cells store some cholesterol, although glycolipid accumulation,
particularly GM2 ganglioside, predominates.

25 There is as yet no accepted treatment for NPC disease. Given the observations
supporting NPC disease's origin in a cholesterol metabolism defect, most treatment
attempts have focused on reducing cholesterol storage (Sylvain *et al.*, 1994, *Pediatr.*

Neurol. 10:228-32, Patterson *et al*, 1993, *Neurology*, 43:61-4). However, restricting cholesterol intake or treating patients with a range of cholesterol-lowering drugs has had puzzlingly little effect on the tissue storage levels of this material, and no apparent effect on the disease's progress.

5

The perception in the art is that the glycolipid accumulation component of NPC disease is a secondary effect of the cholesterol metabolism defect component (see for example Chapter 85 in *The Metabolic and Molecular Bases of Inherited Disease*, 7th edition, McGraw-Hill Inc, New York, pp 2625-2639 (1995), Loftus *et al*, 1997, *Science*, 277: 232-235). Thus, until now, little attention has focussed on treating this component of the disease.

10

Affected neuronal cells in NPC patients undergo morphologic changes including the development of fibrillar tangles that are structurally similar to those seen in neurodegenerative disorders such as Alzheimer's disease and tuberous sclerosis. The age of onset and the rapidity of neuronal deterioration in NPC patients can vary considerably. The mechanism underlying these neurologic changes is unknown. It has been proposed that elevated levels of GM2, such as that seen in NPC patient neurons, may induce ectopic dendritic proliferation and meganeurite formation (Goodman and Walkley (1996) *Brain Res Dev Brain Res* 93:162-71), and dendritogenesis and neuron changes correlate well with disease severity in a feline model of NPC (March *et al*, 1997).

15

20

The imino sugar N-butyldeoxynojirimycin (NB-DNJ) is a potent inhibitor of alpha-glucosidase 1 (involved in N-glycan synthesis), and an even more potent inhibitor of glucosylceramide glucosyltransferase. NB-DNJ is currently undergoing clinical trials as a treatment for Gaucher and Fabry diseases, glycolipid storage disorders resulting from mutations in glucocerebrosidase and alpha-galactosidase A, respectively (see Figure 1 of the accompanying drawings). The rationale underlying these clinical trials is based on

25

the observation that cells treated with NB-DNJ produce markedly reduced glucosylceramide levels because of the molecule's inhibition of glucosylceramide synthesis (see Figure 1 of the accompanying drawings). Thus, the clinical trials are determining whether patient health benefits could be achieved by balancing a NB-DNJ induced decrease in the rate of glucosylceramide synthesis against the impaired rate of glycolipid clearance seen in Gaucher and Fabry disease patients.

We have now found that neuronal glycolipid storage seen in NPC patients, for instance, may also be reduced by NB-DNJ treatment. As demonstrated herein, NB-DNJ markedly reduces clinical and pathological symptoms in feline and murine models of NPC.

Thus, in a first aspect, the present invention provides the use of an inhibitor of glucosylceramide synthesis in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease.

In the context of the present invention, the term "inhibitor" includes molecules such as N-butyldeoxynojirimycin, N-butyldeoxygalactonojirimycin, N-nonyldeoxynojirimycin and other imino sugar-structured inhibitors of glucosylceramide synthesis. However, in addition, it also includes other inhibitors of glycosylceramide synthesis, including agents such as 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol and structurally related analogues thereof. Furthermore, inhibition can also be achieved by the use of genetic approaches, based on the introduction of nucleic acid coding for proteins or peptides capable of inhibiting glucosylceramide synthesis or antisense sequences or catalytic RNA capable of interfering with the expression of enzymes responsible for glucosylceramide synthesis (e.g. glucosylceramide synthase). A combination of any of the above approaches can be used.

In a second aspect, the present invention provides the use of N-butyldeoxynojirimycin in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease.

- 5 In a third aspect, the present invention provides the use of an agent capable of increasing the rate of neuronal glycolipid degradation in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease. Examples of such agents include enzymes which degrade neuronal glycolipids, e.g. lysosomal hexosaminidases, galactosidases, sialidases and glucosylceramide glucosidase, and molecules which increase the activity of
10 such enzyme. In addition, the agent could comprise a nucleic acid sequence (DNA or RNA) which codes for the enzymes mentioned above, i.e. such sequences could be introduced to increase natural production of such enzymes.

- Lipid metabolism also plays a critical role in other neuronal disorders, such as
15 Alzheimer's disease and epilepsy. As mentioned above, NPC patient neurons present with fibrillar tangles reminiscent of the morphology seen in Alzheimer's disease. Interestingly, GM1 ganglioside binding by amyloid beta-protein induces conformational changes that support its formation of fibrous polymers, and the fibrillar deposition of this protein is an early event in Alzheimer's disease (Yanagisawa *et al* (1995) *Nat Med*
20 1:1062-6, Choo-Smith *et al* (1997) *Biol Chem* 272:22987-90). Thus, decreasing GM1 synthesis with agents such as NB-DNJ could inhibit the fibre formation seen in Alzheimer's disease.

- Thus, in a fourth aspect, the present invention provides the use of an inhibitor of
25 glucosylceramide synthesis in the treatment of Alzheimer's disease.

Thus, in a fifth aspect, the present invention provides the use of an inhibitor of glucosylceramide synthesis in the treatment of epilepsy.

In a sixth aspect, the present invention provides the use of an agent capable of increasing the rate of neuronal glycolipid degradation in the manufacture of a medicament for use in the treatment of Alzheimer's disease or epilepsy.

5

In contrast, preliminary clinical trials have shown that neurodegenerative processes seen with Parkinson's disease, stroke and spinal cord injuries seem to improve by treating patients with GM1 ganglioside (Alter (1998) *Ann N Y Acad Sci* 845:391-401; Schneider (1998) *Ann N Y Acad Sci* 845:363-73; Geisler (1998) *Ann N Y Acad Sci* 845: 374-81). It is possible that co-administering glucosylceramide synthesis inhibitors would provide the clinician greater control over this treatment course. Inhibitors like NB-DNJ would limit patient-specific inconsistencies by blocking their neuronal glycolipid synthesis. In addition, inhibiting glucosylceramide synthesis would limit the metabolism of administered glycolipids into other, perhaps unproductive, forms. Thus, the ability to modulate glucosylceramide synthesis with inhibitors such as NB-DNJ may be useful in treatment of a wide variety of neuronal disorders.

According to an eighth aspect of the present invention, there is provided the use of an inhibitor of glucosylceramide synthesis in the production of a medicament for the treatment of a condition treatable by the administration of a ganglioside such as GM1 ganglioside. Examples of such conditions are Parkinson's disease, stroke and spinal-cord injuries.

The medicament may further comprise a ganglioside such as GM1 ganglioside.

25

The invention also provides, in a ninth aspect, a product comprising an inhibitor of glucosylceramide synthesis and a ganglioside (preferably GM1 ganglioside) as a

combined preparation for simultaneous, sequential or separate use in the treatment of a condition treatable by the administration of a ganglioside, such as GM1 ganglioside.

5 Methods and processes for the production of N-butyldeoxynojirimycin can be found for example in US-A-4182767, EP-B-0012278, EP-A-0624652, US-A-4266025, US-A-4405714 and US-A-5151519 for example.

In other aspects, the present invention provides:

- 10 (a) a method for the treatment of Niemann-Pick type C disease which comprises administering to a subject in need thereof a therapeutically effective amount of a glucosylceramide synthesis inhibitor;
- (b) a method for the treatment of Niemann-Pick type C disease which comprises
15 administering to a subject in need thereof a therapeutically effective amount of N-butyldeoxynojirimycin;
- (c) a method for the treatment of Niemann-Pick type C disease which comprises administering to a subject in need thereof a therapeutically effective amount of an agent capable of increasing the rate of degradation of neuronal glycolipids;
- (d) a method for the treatment of Alzheimer's disease or epilepsy which comprises
20 administering to a subject in need thereof a therapeutically effective amount of a glucosylceramide synthesis inhibitor;
- (e) a method for the treatment of Alzheimer's disease or epilepsy which comprises administering to a subject in need thereof a therapeutically effective amount of N-butyldeoxynojirimycin;
- 25 (f) a method for the treatment of Alzheimer's disease or epilepsy which comprises administering to a subject in need thereof a therapeutically effective amount of an agent capable of increasing the rate of degradation of neuronal glycolipids;

- (g) a method for the treatment of a condition treatable by the administration of a ganglioside, such as GM1 ganglioside, which comprises administering to a subject in need thereof a therapeutically effective amount of a glucosylceramide synthesis inhibitor;
- 5 (h) a method for the treatment of a condition treatable by the administration of a ganglioside such as GM1 ganglioside which comprises administering to a subject in need thereof a therapeutically effective amount of N-butyldeoxynojirimycin;
- (i) a method for the treatment of a condition treatable by the administration of a ganglioside such as GM1 ganglioside which comprises administering to a subject
- 10 in need thereof a therapeutically effective amount of an agent capable of increasing the rate of degradation of neuronal glycolipids.

The medicaments described herein and which are also for use in the methods provided herein, may include one or more of the following: preserving agents, solubilising agents,

15 stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odourants, salts, buffers, coating agents or antioxidants. They may also contain therapeutically active agents in addition to the compounds and/or agents described herein.

Routes of Administration

- 20 The medicaments may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such a composition may be prepared by any method known in the art of pharmacy, for example by admixing the active ingredient with a carrier
- 25 under sterile conditions.

Various routes of administration will now be considered in greater detail:

- (i) *Oral Administration*

Medicaments adapted for oral administration may be provided as capsules or tablets; as powders or granules; as solutions, syrups or suspensions (in aqueous or non-aqueous liquids); as edible foams or whips; or as emulsions.

- 5 Tablets or hard gelatine capsules may comprise lactose, maize starch or derivatives thereof, stearic acid or salts thereof.

Soft gelatine capsules may comprise vegetable oils, waxes, fats, semi-solid, or liquid polyols etc.

10

Solutions and syrups may comprise water, polyols and sugars. For the preparation of suspensions oils (e.g. vegetable oils) may be used to provide oil-in-water or water-in-oil suspensions.

- 15 (ii) *Transdermal Administration*

Medicaments adapted for transdermal administration may be provided as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis (Iontophoresis is described in *Pharmaceutical Research*, 3(6):318 (1986)).

20

- (iii) *Topical Administration*

Medicaments adapted for topical administration may be provided as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

- 25 For infections of the eye or other external tissues, for example mouth and skin, a topical ointment or cream is preferably used. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base.

Alternatively, the active ingredient may be formulated in a cream with an oil-in-water base or a water-in-oil base.

5 Medicaments adapted for topical administration to the eye include eye drops. Here the active ingredient can be dissolved or suspended in a suitable carrier, e.g. in an aqueous solvent.

10 Medicaments adapted for topical administration in the mouth include lozenges, pastilles and mouthwashes.

(iv) *Rectal Administration*

Medicaments adapted for rectal administration may be provided as suppositories or enemas.

(v) *Nasal Administration*

15 Medicaments adapted for nasal administration which use solid carriers include a coarse powder (e.g. having a particle size in the range of 20 to 500 microns). This can be administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nose from a container of powder held close to the nose.

20 Compositions adopted for nasal administration which use liquid carriers include nasal sprays or nasal drops. These may comprise aqueous or oil solutions of the active ingredient.

25 Medicaments adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of apparatus, e.g. pressurised aerosols, nebulisers or insufflators. Such apparatus can be constructed so as to provide predetermined dosages of the active ingredient.

(vi) *Vaginal Administration*

Medicaments adapted for vaginal administration may be provided as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

(vii) Parenteral Administration

5 Medicaments adapted for parenteral administration include aqueous and non-aqueous sterile injectable solutions or suspensions. These may contain antioxidants, buffers, bacteriostats and solutes which render the compositions substantially isotonic with the blood of an intended recipient. Other components which may be present in such compositions include water, alcohols, polyols, glycerine and vegetable oils, for example. Compositions adapted
10 for parenteral administration may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, e.g. sterile water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

15

Dosages

Dosages will be readily determinable by routine trials, and will be under the control of the physician or clinician. The guiding principle for determining a suitable dose will be delivery of a suitably efficacious but non-toxic, or acceptably toxic, amount
20 of material. For NB-DNJ or a similar compound, a daily dosage for an adult could be expected to be in the range of from 1 mg to 2 g of active agent, and may be in the range of from 100 to 800 mg, or 300 to 600 mg. The dosage may be administered in a single daily dose or alternatively in two, three or more doses during the day.

25 Preferred features of each aspect of the invention are as for each of the other aspects. *mutatis mutandis*.

In the accompanying drawings:

Figure 1 is a schematic representation of the synthesis and degradation of glucosylceramide-containing glycolipids. Examples of genetic diseases resulting from a defect in one of the enzymes required for glycolipid degradation are indicated. The enzyme reaction inhibited by N-butyldeoxynojirimycin to decrease the synthesis of glucosylceramide-containing glycolipids is also shown.

The invention will now be described with reference to the following examples, which should not in any way be construed as limiting the scope of the invention.

10

EXAMPLES

Example 1 – Inhibition of clinical and pathological symptoms in a feline model of NPC

15

A domestic cat model of Niemann-Pick C has been described that demonstrates the disorder's characteristic liver storage of cholesterol, glucosylceramide, lactosylceramide and phospholipids, and neuronal storage of GM2 and GM3 gangliosides (Lowenthal *et al* (1990) *Acta Neuropathol. (Berl)* 81:189-197). A breeding colony for this animal model of NPC is being maintained to study the disease and its potential treatments (Brown *et al* (1996) *J. Inherit Metab. Dis.* 19:319-330;). NPC cats exhibit clinical signs of the disease beginning around 2-3 months with ataxia and titubation, and progress to severe ataxia and death by around 10-12 months.

From seven feline NPC carrier litter mates, normal and NPC-affected male and female cats were selected for the study. The affected female and unaffected male began treatment with NB-DNJ at 1200 mg/kg/day. This administration level proved to be acutely hepatotoxic to the cats, so the treatments quickly had to be ceased. During a

25

brief recovery period for these animals, an unrelated normal cat was treated to determine the maximum tolerated dose for NB-DNJ in this species. Based on this dose-ranging work, the NPC-affected and unaffected litter mates were restarted with NB-DNJ at 50 mg/kg/day. Over the following weeks, the administration level was increased to 150 mg/kg/day. This dose, too, proved to be hepatotoxic, so the administration level was maintained thereafter at 100 mg/kg/day. Except for brief intervals when the treatments were withheld because of transient appetite loss, the NB-DNJ dosages were continued for about three months. On this date, the animals were sacrificed for histologic and lipid analyses.

10

The following sections highlight the medical and neurologic findings for the study animals.

Cat number: S219

15 *Status: Normal, non-treated*

Date of Birth: 4 Nov., 1997

Gender: Male

This cat had an unremarkable developmental course throughout the treatment period, with normal behaviour, mobility and reflexes. He also underwent a normal weight gain, reaching about 3.6 kg by the end of the treatment period. He was not subjected to neurologic assessments during the treatment period.

20

Cat number: S218

Status: Normal, NB-DNJ-treated

25 *Date of Birth: 4 Nov., 1997*

Gender: Female

This cat had an unremarkable developmental course before her treatment period with NB-DNJ began. Her starting dose of 1200 mg/kg/day of NB-DNJ proved to be acutely

hepatotoxic, causing a dramatic elevation in her serum levels of liver enzymes. She appeared to fully recover from the hepatotoxicity following a two week non-treatment period, so she was restarted on NB-DNJ at an eventual dosage of 100 mg/kg/day. During the remaining course of the treatment period, she exhibited some symptoms which appeared to be drug-related. Her appetite was significantly less than that of a normal cat, requiring her to be hand-fed during some intervals. Her weight gain reflected her depressed appetite, as she weighed only about 2.4 kg at the end of the treatment period. A normal female cat would be expected to weigh about 4 kg at a similar age. However, while she was exceptionally small for her age, she did not show symptoms of emaciation (e.g. muscle wasting, lethargy). Her hair colour also appeared to be affected by the NB-DNJ treatment. Her fur became markedly more beige than any other cat in the colony during the course of the treatments, even more so than the other NB-DNJ-treated animal (S222, see below). She was not subjected to neurologic assessments during the treatment period.

15

Cat number: S221

Status: NPC-affected, non-treated

Date of Birth: 4 Nov., 1997

Gender: Male

20 This cat had an unremarkable developmental course until he began exhibiting the characteristic head tremors and ataxia of feline NPC at about 10 weeks of age. Over the course of the next 20 weeks, his disease symptoms slowly worsened. By the end of the treatment period, he exhibited marked ataxia and head tremors, and required hand-feeding to maintain body weight. The following is a tabulation of his neurologic and
25 medical findings:

Animal S221 - Affected, non-treated

Week	Front leg Hopping	Rear leg hopping	Vision - menace	Ataxia	Intention Tremors	Weight (gms)*
6.5	2	2	2	none	None	544
12.5	2	2	0.5	none	Mild	994
16	2	2	1	none	Mild	1529
18.5	2	1.5	1	none	Mod	1780
20.5	2	2	2	mild	Mod	1906
22.5	2	1.5	0.5	mild	Mod	1990
24.5	2	1.5	0.5	-	Mod	2090
26.5	2	1.5	0.5	mod	Mod	2140
29	2	1.5	0.5	mild	Mod	2270
30.5	1.5	1	0.5	mod	Mod	2337
32.5	2	1	0.5	mild	Mod	2448

* measured within 10 days before corresponding neuronal assessment

Cat number: S222

Status: NPC-affected, NB-DNJ-treated

5 *Date of Birth: 4 Nov., 1997*

Gender: Female

This cat had an unremarkable developmental course until she began exhibiting the characteristic head tremors and ataxia of feline NPC at about 10 weeks of age. She also was noted to have bilateral luxating patellas at about the same time. As with S218, her starting dose of 1200 mg/kg/day of NB-DNJ was acutely hepatotoxic. After a no-treatment recovery period, her eventual dosage of NB-DNJ at 100 mg/kg/day was reasonably well handled. Her appetite was significantly reduced relative to both normal and NPC-affected cats, requiring her to be hand-fed often. Over the course of the next 20 weeks, her disease symptoms slowly worsened. However, on several occasions it was noted by the consulting neurologist that her symptoms were less severe than those of

S221. As with her affected sib, by the end of the protocol she exhibited significant ataxia and head tremors, and she required continual hand-feeding. She too had the light-coloured fur effect of NB-DNJ treatment that was noted for S218. The following is a tabulation of her neurologic and medical findings:

5

Animal S222 - Affected, NB-DNJ-treated						
Week	Front leg Hopping	Rear leg hopping	Vision - Menace	Ataxia	Intention tremors	Weight (gms)*
6.5	2	2	2	none	none	522
12.5	2	2 [†]	1	none	mild	965
16	2	2	1	none	mild	1265
18.5	2	1.5	1.5	none	mild	1390
20.5	2	2	.5	none	mod	1453
22.5	1.5	1.5	1	none	mild	1469
24.5	2	2	1	none	mod	1495
26.5	2	1.5	1	none	mild	1525
29	2	1	1	mod	mod	1565
30.5	-	-	1	mild	mod	1590
32.5	1	1	0.5	mod	mod	1677

* measured within 10 days before corresponding neuronal assessment

[†] diagnosed with bilateral luxating patellas

Cat number: S161

10

Status: Normal, NB-DNJ-treated

Date of Birth: 17 July, 1995

Gender: Female

This cat, unrelated to the four others in the study, was included in the study to range the maximum tolerated dose of NB-DNJ in this species. Her development was unremarkable

at the time when the treatments began, save for the fact that she had a grade 3/4 heart murmur due to valvular insufficiency. She began treatment with 50 mg/kg/day of NB-DNJ on 15 March, 1998. Increasing her dose to 200 mg/kg/day brought on symptoms of lethargy, g.i. distress and increased levels of liver enzymes into her serum. Her dosage
5 was decreased to 100 mg/kg/day for the duration of the treatment period. While her appetite and overall responsiveness were decreased at this dose level, her health was sufficiently robust to maintain the treatments. Nonetheless, towards the end of the treatment period, she needed to be hand-fed to maintain her body weight. Thus, NB-DNJ treatment qualitatively delays the symptoms of neurologic degeneration typical for
10 NPC in cats.

The following sections highlight the histologic and lipid analysis findings for the study animals. As with humans, there is an increased expression of gangliosides in feline NPC neurons. Immunocytochemistry demonstrates numerous ganglioside immunoreactive
15 neurons in the cerebral cortex and cerebellum. There is a corresponding increase in neuronal ganglioside level and histology changes seen in NPC humans. Importantly, NPC cats exhibit ectopic dendrite growth similar to that seen in human children with this disease (March *et al* (1997) *Acta Neuropathol.* 94:164-172).

20 Immunocytochemical studies with anti-GM2 ganglioside antibodies were used to probe for ganglioside expression in treated vs. untreated cats in a qualitative manner. Both normal cats, regardless of treatment status, did not display GM2 immunoreactivity in pyramidal cells of the cerebral cortex, Purkinje cells, or cells within the granular layer of the cerebellum. In the NPC cat that was not treated with NB-DNJ, punctate vesicular
25 GM2 labelling was extensive and intensely labelled numerous pyramidal cells of the cerebral cortex which also displayed meganeurites. Also, Purkinje cells of the cerebral cortex and the entire granular cell layer displayed extensive GM2 labelling. In the NPC cat treated with NB-DNJ, GM2 labelling was observed in the cerebral cortex, but was

qualitatively less severe compared to the untreated cat. In the cerebellum, the granular cell layer was largely devoid of GM2 immunoreactivity, suggesting that ganglioside storage had been qualitatively diminished relative to that seen in the untreated NPC cat. Purkinje cells also demonstrated qualitatively less GM2 labelling. Thus, NB-DNJ treatment qualitatively decreases the accumulation of glucosylceramide-containing glycolipids (e.g. GM2) typical for NPC in cats.

Example 2 – Inhibition of clinical and pathological symptoms in a mouse model of NPC

Colonies of mutant mice expressing the NPC phenotype have been described (Pentchev *et al.*, 1984, Miyawaki *et al.*, 1986; Kitagawa, 1987), and has been validated by a number of criteria as an authentic model of the disease (Akaboshi *et al.*, 1997). NPC mice display clinical signs of the disease around 6-8 weeks of age with mild intention tremor and ataxia. By 9 weeks, the mice exhibit severe ataxia, tremors and weight loss. Death results by 10-12 weeks.

The brains of NPC mice are grossly normal. However, microscopic examination reveals swollen somata, meganeurite formation and enlarged axon hillock regions of cortical pyramidal neurons. Meganeurites and neuritic tufts appear in amygdala neuron. White matter and Purkinje cells display axonal spheroids. Anti-ganglioside antibody staining shows increased GM2 levels primarily in laminae II/III and V pyramidal neurons, and astrocytes in layer I. GD2 levels are elevated in pyramidal neurons throughout the cerebral cortex. Moderate increases are also seen for level of GM3 in layer VI, and GM1 in pyramidal neurons. There is no corresponding change in CD3 or asialo-GM2 levels in NPC mouse brains.

Breeding pairs of mice heterozygous for the mutation causing NPC were used to produce offspring that are NPC^{-/-} homozygotes. These animals, along with their normal wildtype

littermates, were used in the following NB-DNJ drug study. Where indicated, NB-DNJ was administered daily by mixing with ground mouse chow. Mice were PCR genotyped 2-3 weeks of age to determine their genetic background.

- 5 Ten NPC^{-/-} mice, with ages ranging from 3-7 weeks, were entered into a treatment study. Seven were treated with 1200 mg/kg/day and six were untreated. Regardless of treatment, NPC mice between the ages of 0-5 weeks did not display any features of the NPC phenotype. However, by 8 weeks of age, 5 out of 6 untreated NPC^{-/-} mice displayed the clinical phenotype of their disease (intention tremor, ataxia), while none of the NB-DNJ displayed any symptoms of neurologic effects. All six of the untreated mice showed severe neurologic impairment by 9 weeks of age, whereas only 4 of 7 NB-DNJ treated mice displayed any degree of symptoms. By 10 weeks of age, all six untreated NPC^{-/-} mice died or were sacrificed according to veterinary animal care requirements. In contrast, 4 of 7 NPC^{-/-} mice treated with NB-DNJ lived into their twelfth week. Three of these four surviving mice displayed some degree of NPC-induced neural degeneration, while one appeared normal. In this experiment, untreated NPC^{-/-} mice survived 65 ± 1 days (average \pm SE; $n = 6$), while NPC^{-/-} mice treated with NB-DNJ at 1200 mg/kg/day survived 88 ± 4 days ($n = 7$). Thus, NB-DNJ treatment increase longevity in NPC mice by 26% in this study, as well as qualitatively delaying the symptoms of neurologic degeneration typical for NPC in mice.
- 10
- 15
- 20

CLAIMS:

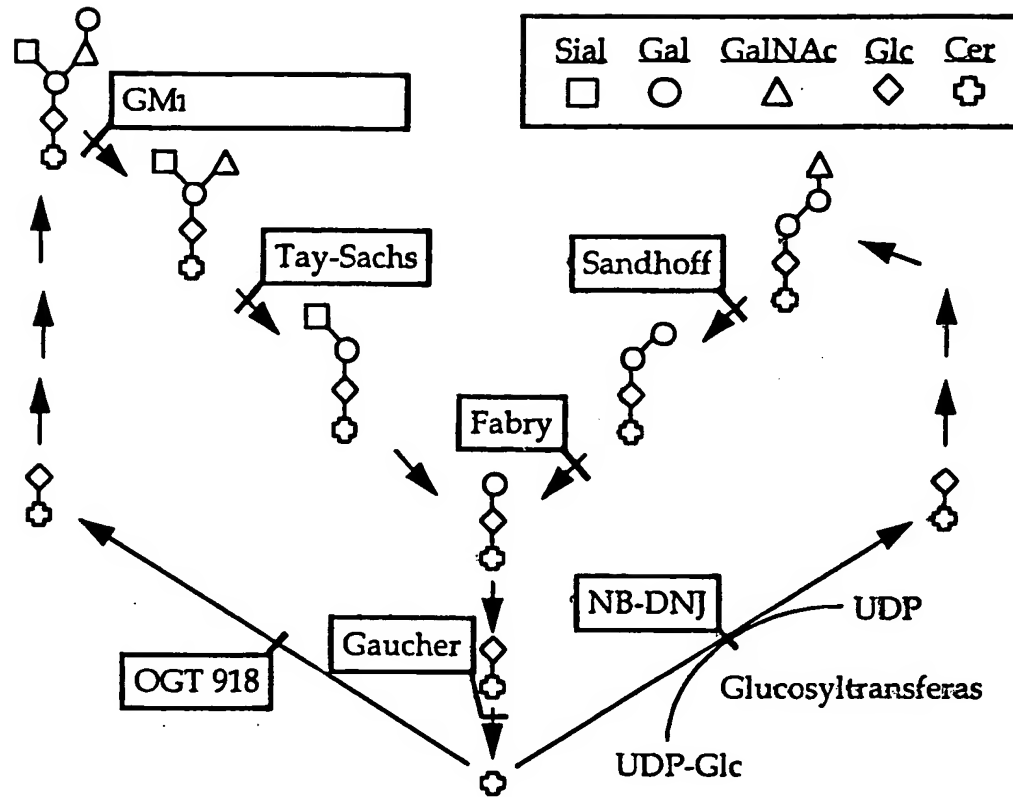
1. The use of an inhibitor of glucosylceramide synthesis in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease.
2. The use of an inhibitor of glucosylceramide synthesis in the treatment of Alzheimer's disease.
3. The use of an inhibitor of glucosylceramide synthesis in the treatment of epilepsy.
4. The use as claimed in claim 1, 2 or 3, wherein the inhibitor is one or more imino sugar-structured inhibitors of glucosylceramide synthesis.
5. The use as claimed in claim 4, wherein the inhibitor comprises one or more of N-butyldeoxynojirimycin, N-butyldeoxygalactonojirimycin and N-nonyldeoxynojirimycin.
6. The use as claimed in any preceding claim, wherein the inhibitor comprises 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol or a structurally related analogue thereof.
7. The use as claimed in any preceding claim, wherein the inhibitor comprises one or more of a nucleic acid coding for a protein or peptide capable of inhibiting glucosylceramide synthesis, and an antisense sequence or catalytic RNA capable of interfering with the expression of enzymes responsible for glucosylceramide synthesis.
8. The use of N-butyldeoxynojirimycin in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease.

9. The use of an agent capable of increasing the rate of neuronal glycolipid degradation in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease.
- 5 10. The use of an agent capable of increasing the rate of neuronal glycolipid degradation in the manufacture of a medicament for use in the treatment of Alzheimer's disease.
- 10 11. The use of an agent capable of increasing the rate of neuronal glycolipid degradation in the manufacture of a medicament for use in the treatment of epilepsy.
- 15 12. The use as claimed in claim 9, 10 or 11, wherein the agent comprises one or more of an enzyme which degrades neuronal glycolipids, a molecule which increases the activity of such an enzyme, and a nucleic acid sequence (DNA or RNA) which codes for such an enzyme.
- 20 13. The use of an inhibitor of glucosylceramide synthesis in the production of a medicament for the treatment of a condition treatable by the administration of a ganglioside.
14. The use as claimed in claim 13, wherein the condition is treatable by the administration of GM1 ganglioside.
- 25 15. The use as claimed in claim 13 or claim 14, wherein the condition is Parkinson's disease, stroke or a spinal cord injury.
16. The use as claimed in claim 13, 14 or 15, wherein the medicament further comprises a ganglioside.

17. The use as claimed in claim 16, wherein the ganglioside is GM1 ganglioside.
18. A product comprising an inhibitor of glucosylceramide synthesis and a
5 ganglioside as a combined preparation for simultaneous, sequential or separate use in the
treatment of a condition treatable by the administration of a ganglioside.
19. A product as claimed in claim 18, wherein the ganglioside is GM1 ganglioside.

1/1

FIGURE 1



INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/GB 00/01563

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/445 A61K31/5375 A61P3/00 A61P25/00 A61P25/08
 A61P25/16 A61P25/28 A61P9/10 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE, WPI Data, PAJ, BIOSIS, CANCERLIT,
 AIDSLINE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 02161 A (VIANELLO PAOLA ;KOOMEN GERRIT JAN (NL); AERTS JOHANNES MARIA FRANC) 22 January 1998 (1998-01-22) abstract	1,4
A	page 1, line 1 - line 5 page 2, line 32 - page 3, line 3 page 4, line 15 - line 17 page 8, line 26 - line 36 page 9, line 24 - line 26 page 14, line 6 - line 17 page 14, line 31 - line 36 page 23, line 5 - line 18 claims 12-15	5,8,9

	--/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not
 considered to be of particular relevance

"E" earlier document but published on or after the international
 filing date

"L" document which may throw doubts on priority claim(s) or
 which is cited to establish the publication date of another
 citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or
 other means

"P" document published prior to the international filing date but
 later than the priority date claimed

"T" later document published after the international filing date
 or priority date and not in conflict with the application but
 cited to understand the principle or theory underlying the
 invention

"X" document of particular relevance; the claimed invention
 cannot be considered novel or cannot be considered to
 involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention
 cannot be considered to involve an inventive step when the
 document is combined with one or more other such docu-
 ments, such combination being obvious to a person skilled
 in the art.

"8" document member of the same patent family

Date of the actual completion of the international search

15 September 2000

Date of mailing of the international search report

06/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Cielen, E

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PLATT F M ET AL: "NEW THERAPEUTIC PROSPECTS FOR THE GLYCOSPHINGOLIPID LYSOSOMAL STORAGE DISEASES" BIOCHEMICAL PHARMACOLOGY, GB, PERGAMON, OXFORD, vol. 56, no. 4, 1998, pages 421-430, XP000886851 ISSN: 0006-2952 abstract figures 1,2 page 423, column 2, paragraph 2 page 424, column 1, paragraph 3 -column 2, paragraph 2 page 425, column 2, paragraph 2 page 426, column 1, paragraph 1 -page 427, column 1, paragraph 3 page 429, column 1, paragraph 2 ---</p>	1,4-6,8
Y	<p>US 5 798 366 A (BUTTERS TERRY D ET AL) 25 August 1998 (1998-08-25) abstract column 1, line 26 - line 32 column 1, line 65 -column 2, line 59 column 7, line 12 - line 42 ---</p>	1,4-6,8
Y	<p>PLATT F M ET AL: "PREVENTION OF LYSOSOMAL STORAGE IN TAY-SACHS MICE TREATED WITH N-BUTYLDEOXYNOJIRIMYCIN" SCIENCE, US, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 276, no. 5311, 18 April 1997 (1997-04-18), pages 428-431, XP002065772 ISSN: 0036-8075 abstract page 429, column 1, paragraph 2 - paragraph 3 page 430, column 3, paragraph 3 -page 431, column 1, paragraph 1 --- -/--</p>	1,4,5,8

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PLATT F M ET AL: "N-BUTYLDEOXYGALACTONOJIRIMYCIN INHIBITS GLYCOLIPID BIOSYNTHESIS BUT DOES NOT AFFECT N-LINKED OLIGOSACCHARIDE PROCESSING" JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 269, no. 43, 28 October 1994 (1994-10-28), pages 27108-27114, XP002065777 ISSN: 0021-9258 abstract page 27108, column 1, paragraph 2 -column 2, paragraph 3 page 27110, column 2, paragraph 2 page 27111, column 1, paragraph 3 -column 2, paragraph 1 page 27114, column 1, paragraph 4 -column 2, paragraph 1</p>	1,4,5,8
Y	<p>M. H. BEERS, R. BERKOW: "The Merck Manual of Diagnosis and Therapy Seventeenth Edition" 1999, MERCK RESEARCH LABORATORIES, NEW YORK XP002147345 page 212 -page 216</p>	1,4-6,8
X	<p>RÖSNER HARALD: "Significance of gangliosides in neuronal differentiation of neuroblastoma cells and neurite growth in tissue culture." ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 845, 16 June 1998 (1998-06-16), pages 200-214, XP000937684 abstract page 200, paragraph 2 page 201, paragraph 3 page 204, paragraph 3 table 1 page 206, paragraph 2 page 209, paragraph 1 - paragraph 2 page 210, paragraph 1 page 211, paragraph 3 page 212, paragraph 3 -page 213, paragraph 1</p> <p style="text-align: center;">--- -/--</p>	13-19

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	MEUILLET E J ET AL: "Modulation of EGF receptor activity by changes in the GM3 content in a human epidermoid carcinoma cell line, A431." EXPERIMENTAL CELL RESEARCH, (2000 APR 10) 256 (1) 74-82. , XP000937516	13,16,18
P, A	abstract page 75, column 1, paragraph 1 page 78, column 2, paragraph 1 -page 79, column 1, paragraph 1 page 79, column 2, paragraph 1 -----	14,17,19
E	WO 00 33843 A (UNIV OXFORD ;BUTTERS TERRY D (GB); DWEK RAYMOND A (GB); PLATT FRAN) 15 June 2000 (2000-06-15) abstract page 3, paragraph 1 - paragraph 2 page 5, paragraph 3 page 7, paragraphs 2,4 claims 1-3 -----	1,4,5,8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-4,7,13-19 relate to a compounds, compositions and their therapeutic uses defined by reference to a desirable characteristic or property, namely "an inhibitor of glucosylceramide synthesis". Moreover, claim 7, claims 9-12 relate to compounds and their therapeutic uses defined by reference to the desirable characteristics or properties "a nucleic acid coding for a protein or peptide capable of inhibiting glucosylceramide synthesis", "an antisense sequence or catalytic RNA capable of interfering with the expression of enzymes responsible for glucosylceramide synthesis", "an agent capable of increasing the rate of neuronal glycolipid degradation", "an enzyme which degrades neuronal glycolipids", "a molecule which increases the activity of such an enzyme", "a nucleic acid sequence (DNA or RNA) which codes for such an enzyme".

The claims cover all compounds, compositions and their therapeutic uses having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds, compositions and their therapeutic uses. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds, compositions and their therapeutic uses by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Moreover, present claims 13-14,16-19 relate to a therapeutic application defined as "a treatment of a condition treatable by administration of a ganglioside". The definition is not a clear and unequivocal description of a therapeutic application. The expression "a structurally related analogue" is vague and indeterminate (claim 6).

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds for which pharmaceutical data are provided in the examples and the compounds specifically mentioned in claims 5, 6, 8 and the diseases specifically mentioned in claims 1-3, 8-11 and 15, with due regard to the general idea underlying the application.

Claims searched partially: 1-19.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01563

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9802161	A	22-01-1998	AU 3464797 A EP 0912179 A	09-02-1998 06-05-1999
US 5798366	A	25-08-1998	US 5656641 A US 5786368 A US 5580884 A US 5399567 A AU 5813898 A EP 1007043 A WO 9830219 A US 5786369 A US 5801185 A AT 148456 T AU 6783294 A CA 2159988 A DE 69401658 D DE 69401658 T DK 698012 T EP 0698012 A ES 2097653 T GR 3022554 T JP 8510244 T WO 9426714 A US 5472969 A US 5525616 A	12-08-1997 28-07-1998 03-12-1996 21-03-1995 03-08-1998 14-06-2000 16-07-1998 28-07-1998 01-09-1998 15-02-1997 12-12-1994 24-11-1994 13-03-1997 12-06-1997 17-02-1997 28-02-1996 01-04-1997 31-05-1997 29-10-1996 24-11-1994 05-12-1995 11-06-1996
WO 0033843	A	15-06-2000	NONE	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☒ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.